REMARKS

Claims 1 – 16, and 30 – 33 are pending and under consideration in the instant examination. Claims 34–43 are withdrawn. Applicants added claims 44–50 in an after-final amendment and response, filed October 16, 2003, but these claims were not entered. With this amendment, Applicants introduce new claims 51 – 62.

Applicants kindly thank the Examiner for her courtesies extended during telephonic interviews with Applicants' representative, Richard G. A. Bone, on October 15, 2003, and on December 4, 2003. Applicants draw the Examiner's attention to respective statements of substance of interview, filed November 12, 2003, and on even date herewith.

Amendments to the Specification

Applicants have amended the specification to insert a reference to SEQ ID NO's of various portions of the structural coordinates presented in Appendix 2 of the specification. Since the Examiner objected to, and has not entered, Applicants' amendments of the same paragraph that was presented in their Amendment and Response of November 18, 2002, the amendment presented herein shows mark-ups with respect to the specification as filed, as if no previous amendments to the same paragraph had been carried out.

Applicants have also amended the specification to correct a reference to a SEQ ID NO: of a sequence in Appendix 3.

As discussed hereinbelow, no new matter has been added by way of this Amendment and entry thereof is respectfully requested.

Amendments to the Claims

Applicants respectfully request consideration of the various amendments presented herein, which Applicants believe will bring the subject application into condition for allowance.

Applicants have amended claim 1 to recite a test compound in the singular, as opposed to the plural ("compounds"), and also to correct a minor issue of antecedent basis, in an effort to improve the clarity of the claim.

Applicants have amended claims 2 – 8 to attend to issues raised by the Examiner in respect of the identification of sequences by SEQ ID NO, as further discussed hereinbelow.

Applicants have also amended the list of residues in claim 8; the amended list finds support in the specification as filed at page 9, lines 26 – 28, and at page 47, lines 16 – 18.

Applicants have amended claim 16 to delete the parenthetic term "(NR-box)" which is now superfluous in light of the full recitation of the term "nuclear receptor box" in the same claim.

Finally, Applicants respectfully request consideration of new claims 51 – 62, depending directly or indirectly from claim 1, which recite further limitations of the atomic structural model of claim 1. Such claims find support in the specification as filed. In particular, the atomic structural model of claim 51 is supported the model presented in Appendix 1 of the specification. The homologue limitation of claim 51 is supported by the specification as filed at page 18, lines 12 – 14, and also by claim 18 as originally filed.

Claim 52 is similarly supported by the structures of Appendices 1 – 3 of the specification as filed, as well as by the experimental protocols reported in Examples 15 and 16 of the specification as filed (see pages 36 – 42). Claim 53 is supported by the specification as filed at page 18, lines 14 – 15.

Claims 54 – 55 are supported by the structural models of TRβ and ERα LBD's with a GRIP1 NR-box 2 peptide bound to the respective coactivator binding sites, described at pages 36 – 42 of the specification as filed.

Claims 56 and 57 are supported by Examples 12 and 13, presented in the specification as filed at pages 32 – 33, in particular at page 32, lines 17 –28.

Claim 58 recites that the atomic structural model comprises atomic coordinates of amino acids that form a hydrophobic cleft of the coactivator binding site, and finds support in the specification as filed, see for example, at page 9, second full paragraph.

Claim 59 recites an additional limitation that the test compounds interacts with the amino acid residues form the hydrophobic cleft, and finds support at page 11, lines 20 –21 of the specification as filed.

Claim 60 recites an additional limitation that the test compound interacts with at least one of the amino acid residues form the hydrophobic cleft. This limitation is supported by the specification as filed at, for example, page 14, first paragraph. At this part of the specification, compounds that fit in the hydrophobic cleft are discussed. In particular, such

compounds "can be designed to contain hydrophobic groups that interact with hydrophobic residues of the coactivator binding site" (page 14, lines 9–11). The remainder of this paragraph indicates that such compounds can be constructed to mimic a NR-box 2 peptide that has a hydrophobic motif that itself forms interactions with hydrophobic residues in the coactivator binding site. Finally, the paragraph concludes that "[s]mall organic molecules that mimic one or more of these particular interactions also can be designed", thereby suggesting that molecules that bind need not interact with all the amino acid residues that form the hydrophobic cleft. Accordingly, Claim 60 is supported by the specification as filed.

Claim 61 recites the method of any one of claims 2 – 8, wherein the test compound interacts with amino acid residues that form a hydrophobic cleft in the coactivator binding site. Claims 2 – 8 recite that the amino acid residues are identified by homology with residues of SEQ ID Nos 52 or 53. As found in the specification (as amended herein), pages 36 – 37, the structure presented in Appendix 1 (whose sequence is found in SEQ ID NO's 52 and 53) comprises residues K211–P254, and G261–D461 which includes those hydrophobic residues in the coactivator binding site. Accordingly, Claim 61 is supported by the specification as filed.

Claim 62 recites the method of any one of claims 2 – 8, wherein the test compound interacts with the recited amino acid residues. Support for interaction with the residues enumerated in claim 2 can be found in the specification as filed at, for example, page 10, lines 30 –31. However, one of ordinary skill in the art would understand, reading the specification in its entirety, that the interaction between a test compound and any recited set of residues in the coactivator binding site is contemplated. For example, the specification at page 9 sets forth the structure of the coactivator binding site and its constituent residues. Pages 10 –11 describe, without limitation, computational methods of designing molecules that bind to residues within the coactivator binding site. The specification at page 12 indicates that different compounds may interact with different residues within the coactivator binding sites of different nuclear receptors. At page 14, first paragraph, it is stated that compounds can be designed to mimic one or more of the interactions of known coactivator peptides. The combination of such teachings would demonstrate to one of ordinary skill in the art that interaction between a test compound and various of the sets of amino acids forming the coactivator binding site would be within the scope of the present invention.

Accordingly, Applicants respectfully submit that no new matter is being introduced in claims 51 – 62, and entry thereof is respectfully requested.

Elections and Restrictions

Applicants have reviewed the Examiner's remarks concerning her Restriction Requirement, issued February 6, 2003, and Applicants' response thereto, mailed April 7, 2003. Applicants understand that the restriction requirement itself has been withdrawn, but that Applicants' newly-filed claims 34–43 are being withdrawn as being directed to a non-elected invention.

Nevertheless, Applicants wish to take this opportunity to thank the Examiner for the opportunity to discuss the restriction requirement during the telephonic interview of October 15, 2003. In particular, Applicants thank the Examiner for clarifying that Applicants had not in fact presented an argument as to the scope of claim 9 in their response of April 7, 2003, and that claim 1 is considered to be a generic claim.

Objections to the Specification

The Examiner has objected to the amendments to the specification introduced by Applicants in their Amendment and Response filed November 19, 2002, for allegedly introducing new matter.

The objection to the characterization of Appendix 2

The Examiner has objected to Applicants' introduction, on page 42 (to the paragraph beginning at line 36 of page 41) of the specification, of a description of the crystal structure whose coordinates are presented in Appendix 2 of the specification. In particular, the Examiner has pointed out that "residues labeled 'A' include those designated 'DES' and 'CL', while residues labeled 'B' include those designated 'DES' and 'CBM'." Applicants thank the Examiner for bringing this to Applicants' attention and respectfully request consideration of a new form of amendment to the paragraph beginning at line 36 of page 41, in which the specific residues of chain identifiers "A" and "B" that correspond to the human ERα are specifically delineated.

Furthermore, the Examiner has alleged that "one skilled in the art would not be able to deduce, merely by looking at Table [sic] 2, what proteins, peptides, or portions thereof, are represented by residues labeled A, B, C, and D," and has objected to Applicants' statement that the structure in Appendix 2 contains two molecules of DES and two molecules of GRIP1 NR-box 2 peptide. Although Applicants believe that the specification elsewhere provides ample support for the characterization of the structure in question (see, *e.g.*, page 39, line 14,

and at page 41, lines 29–32, of the specification), and that one of ordinary skill in the art would be capable of deducing the structure of various molecules from a PDB file, either by inspection as the Examiner has done, or by using a computer modeling program widely available in the art, Applicants nevertheless have introduced a form of amendment that does not characterize the structure in Appendix 2. Applicants' amendment herein merely identifies which fragments in Appendix 2 correspond to particular SEQ ID NOs. Accordingly entry thereof is respectfully requested.

The objection to SEQ ID NO:53 of the Sequence Listing

Applicants thank the Examiner for pointing out the discrepancy between SEQ ID NO: 53 and chain B of Appendix 1. Upon reviewing the structure in Appendix 1, Applicants note that residue Gly 345 (at p.128 of the specification as filed) was inadvertently not presented in SEQ ID NO: 53 in the sequence listing filed November 19, 2003. Accordingly, Applicants transmit on even date herewith a substitute sequence listing that corrects SEQ ID NO:53. Applicants further note that SEQ ID NO: 52 is also revised in the substitute sequence listing so that residues Gly 261 and Gly 262 are removed and both replaced by Xaa (any amino acid residue). These two residues are absent from chain A of Appendix 1, as called out in the remarks in the header of the PDB file, at page 74 of the specification as filed, and as can be seen further at page 80 of the specification as filed.

The objection to SEQ ID NO:59 of the Sequence Listing

The Examiner is thanked for her observations regarding SEQ ID NOs: 59 and 60. Indeed, references in the specification to SEQ ID NOs: 59 and 60 have been inadvertently transposed. Accordingly, with the amendments to the specification presented herein, it is clarified that SEQ ID NO: 60 corresponds to chain D of Appendix 2, whereas SEQ ID NO: 59 corresponds to the 246-residue portion of ERα presented in Appendix 3. Accordingly, SEQ ID NO: 59 is not new matter, and consideration and entry thereof is respectfully requested.

Rejections of the Claims Under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 2 – 8 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner has objected to the use of parenthesis around two sequence identifiers, and has further suggested that the use of a pair of sequence identifiers with the conjunction "or" renders the meaning of the claim unclear.

Applicants thank the Examiner for her suggestion during the telephonic interview on October 15, 2003, and have amended the claims herewith to delete the parentheses and to insert the list of residues at a different position. Such amendments make it clear that the portion of human thyroid beta receptor in question is that identified by either of the two SEQ ID NOs.

Rejections of the Claims Under 35 U.S.C. § 102(e)

Claims 1–10, 12–15, and 30–33 stand rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by U.S. Patent no. 6,266,622, to Scanlan *et al.*, (hereinafter "Scanlan"). Applicants respectfully traverse the rejection on the grounds that Scanlan is disqualified as a reference. In an amendment and response mailed October 16, 2003, Applicants asserted that Scanlan should no longer be available as a reference on grounds of common ownership. For the Examiner's benefit, Applicants hereby restate this reasoning and respectfully request the Examiner's consideration thereof.

By virtue of the fact that the instant application is a Continued Prosecution Application (CPA) filed July 3, 2001, Applicants respectfully point out that the instant application benefits from the provisions of 35 U.S.C. § 103(c) enacted as part of the American Inventors Protection Act. Accordingly, a commonly owned patent that is cited under 35 U.S.C. § 102(e) is not prior art if it was commonly owned at the time the instant invention was made. The '622 patent is prior art only by virtue of § 102(e) because it was filed before the filing date of the instant application, but issued afterwards (on July 24, 2001). U.S. Patent no. 6,266,622 was owned by the Regents of the University of California at the time that the invention of the instant application, serial no. 09/281,717, was made. The inventors of the instant application were under an obligation to assign their rights in the invention to the Regents of the University of California at the time that the invention was made. Accordingly, the '622 patent is not prior art against the instant application for purposes of 35 U.S.C. § 102(e), and Applicants respectfully request that the rejection of record be removed.

Nevertheless, Applicants state that the foregoing conclusion, that the '622 patent is not prior art, is not to be taken as an admission that the Examiner's remarks concerning the capacity of the '622 patent to anticipate or to render obvious Applicants' instant claims, in her office action mailed July 16, 2003, are correct. In particular, Applicants disagree with the Examiner's assertion that "compounds which result in an increase in activity may be considered coactivators". Although coactivators may result in an increase in activity, other

compounds such as ligands, which do not function in the same way as coactivators, *i.e.*, by binding other than to the coactivator binding site, may also result in an increase in nuclear receptor activity.

Rejections of the Claims Under 35 U.S.C. § 103(a)

Applicants preface the two rejections under 35 U.S.C. § 103(a) with the following remarks.

The Applicants remind the Examiner that she bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, one basic criterion that must be met is that the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); M.P.E.P. § 706.02(j).

Furthermore, as discussed hereinabove, and as also presented in an amendment and response filed by Applicants on October 16, 2003 but which has not been entered, the instant application is a CPA filed July 3, 2001 and therefore benefits from the provisions of 35 U.S.C. § 103(c). According to such provisions, a commonly owned patent that would be cited under 35 U.S.C. § 102(e) is not prior art for purposes of determining non-obviousness under 35 U.S.C. § 103 if it was commonly owned at the time the instant invention was made. The '622 patent is prior art only by virtue of § 102(e) because it was filed before the filing date of the instant application, but issued afterwards (on July 24, 2001). U.S. Patent no. 6,266,622 was owned by the Regents of the University of California at the time that the invention of the instant application, serial no. 09/281,717, was made. The inventors of the instant application were under an obligation to assign their rights in the invention to the Regents of the University of California at the time that the invention was made. Accordingly, the '622 patent is not prior art against the instant application for purposes of 35 U.S.C. § 103(a), and for additional reasons discussed hereinbelow, Applicants respectfully request that the rejections of record be removed.

Rejection over Scanlan in view of Kuntz

Claims 1–15, and 30–33 stand rejected under 35 U.S.C. § 103 (a) as being allegedly obvious over Scanlan in view of Kuntz et al., *Science*, 257, 1078–1082, (1992) (hereinafter "Kuntz"). Applicants respectfully traverse the rejection because the Examiner has not made out a *prima facie* case.

Claim 1 recites a method of identifying compound that binds to a coactivator binding site of a nuclear receptor. As discussed hereinabove, Scanlan is not available as a reference.

Kuntz does not teach methods of identifying compounds that bind to the coactivator binding site of a nuclear receptor; instead, Kuntz teaches generalized computational methods of drug discovery and high throughput screening. Accordingly, Kuntz does not teach each and every limitation of claim 1. Claims 2–15 and 30–33 depend either directly or indirectly from Claim 1 and are thus patentable for at least the same reasons as Claim 1. In view of the foregoing, claims 1–15 and 30–33 are not obvious over Scanlan and Kuntz because the references in combination fail to teach or suggest each and every limitation of the claims. Accordingly, Applicants respectfully request that the rejection of Claims 1–15, and 30–33 under 35 U.S.C. § 103 (a) over Scanlan in view of Kuntz be withdrawn.

Rejection over Scanlan in view of Heery

Claims 1 – 10, 12 – 16, and 30 – 33 stand rejected under 35 U.S.C. § 103 (a) as being allegedly obvious over Scanlan in view of Heery *et al.*, *Nature*, 387, 733–736, (1997) (hereinafter "Heery"). Applicants respectfully traverse the rejection because the Examiner has not made out a *prima facie* case.

Claim 1 recites a method of identifying compound that binds to a coactivator binding site of a nuclear receptor. As discussed hereinabove, Scanlan is not available as a reference. Heery does not teach methods of identifying compounds that bind to the coactivator binding site of a nuclear receptor; instead, Heery teaches that an LxxLL motif is found in nuclear receptor coactivator peptides. Accordingly, Heery does not teach each and every limitation of claim 1. Claims 2–10, 12–16, and 30–33 depend either directly or indirectly from Claim 1 and are thus patentable for at least the same reasons as Claim 1. In view of the foregoing, claims 1–10, 12–16, and 30–33 are not obvious over Scanlan in view of Heery because the references in combination fail to teach or suggest each and every limitation of the claims. Accordingly, Applicants respectfully request that the rejection of Claims 1 – 10, 12 – 16, and 30 – 33 under 35 U.S.C. § 103 (a) over Scanlan in view of Heery be withdrawn.

CONCLUSION

In view of the remarks presented hereinabove, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150 for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: December 16, 2003

Richard G. A. Bone
Limited recognition under 37 C.F.R. § 10.9(b)
(Copy of certificate attached hereto.)

for Samuel B. Abrams Reg. No. 30,605
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, NY 10036-2711
(212) 790-9090

CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. 1.8(a)

I hereby certify that this paper is being filed with the United States Patent and Trademark Office by facsimile transmission on **December 16, 2003** to facsimile telephone number 703-308-4242.

Richard G. A. Bone — December 16, 2003

Richard G. A. Bone — Date